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09/787,082	06/14/2001	David James Craik	DAV1-00015	1285

7590 04/04/2003

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EXAMINER

KAM C CHEUNG

ART UNIT	PAPER NUMBER

DATE MAILED: 04/04/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/787,082	CRAIK ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-18* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of SEQ ID NO:2 as the peptide linker and SEQ ID NO:6 as the cyclic peptide in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the Office Action fails to demonstrate adequate basis for lack of unity, and the common technical feature present throughout the claims is the cyclization of a conotoxin peptide. This is not found persuasive because each peptide with different amino acid sequence has different mode of operation and produce different function or effect, e.g., SEQ ID NOs:5, 6 and 7 are cyclo-MVIIA conotoxins, which are specific to voltage-sensitive calcium channels (Example 3 of the specification), while SEQ ID NOs: 8 and 9 are cyclic MII α-conotoxins, which target Ach receptors (Table 1 of the specification), thus, the peptides with various sequences do not have the same technical features. However, upon reconsideration, SEQ ID NOs: 1-9 will be examined. In the response to the restriction requirement, applicant has amended claims 1-3, 5, 6 and 10-17, therefore claims 1-18 and SEQ ID NOs: 1-9 are examined.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a cyclized conotoxin peptide. As written, the claim does not explicitly indicate the hand of man. Insertion of "synthetically" in connection with a cyclized conotoxin peptide is suggested. See MPEP § 2105.

3. Claims 14 and 16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 and 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cyclic conotoxin peptide such as SEQ ID NOs:5-9 having disulfide bonds and an amide bond linked at N- and C-termini, where the amino acid sequence is defined; a process of preparing the cyclic conotoxin; a composition comprising the cyclic conotoxin; a method of using the cyclic conotoxin having activity at ion channel receptors as a neuropharmacological probe; or, a cyclic conotoxin peptide having disulfide bonds and C-terminus blocked as indicated in the prior art, does not reasonably provide enablement for a cyclized conotoxin peptide having no free N- and C-termini, where the amino acid sequence is not defined; a process of preparing the cyclic conotoxin; a composition comprising the cyclic conotoxin; a method of using the cyclic conotoxin as a neuropharmacological probe; or a method of treatment or prophylaxis of diseases comprising administering the cyclic conotoxin, where the disease is not defined. The specification does not enable a person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9 and 11-18 are directed to a cyclic conotoxin peptide having no free N- and C-termini (claims 1-9); a process of preparing the cyclic conotoxin (claims 11-13); a composition comprising the cyclic conotoxin (claims 17 and 18); a method of using the cyclic conotoxin as a neuropharmacological probe (claim 14); or a method of treatment or prophylaxis of diseases comprising administering the cyclic conotoxin (claims 15 and 16). The specification, however, only discloses cursory conclusions without data supporting the findings, which states that cyclization of the peptide backbone of conotoxin to produce non-natural analogs results in new molecules which can retain the therapeutic activity of the non-cyclized peptide (page 2, lines 9-11). There are no indicia that the present application enables the full scope in view of the cyclized conotoxin peptide having no free N- or C-termini and the method of treating diseases using the conotoxin peptide as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the cyclized conotoxin peptides, and the treating conditions for various diseases using cyclized conotoxin peptides, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples demonstrating the making and use of various cyclized conotoxin peptides except for cyclic MVIIA conotoxins (Examples 1-3, 5) and MII α-conotoxins (Example 6).

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Shon *et al.*, WO 96/33206) indicates μ-conotoxin PIIIA, which is a sodium channel blocker, is useful as active agent for treating urinary or fecal incontinence. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of various cyclized conotoxin peptides besides cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, the treating conditions for various diseases, and the effects of the cyclized conotoxin peptides in the treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a cyclized conotoxin peptide having no free N- and C-termini, and a method of treatment or prophylaxis of diseases comprising administering the cyclic conotoxin. However, the specification does not show any cyclized conotoxin peptide other than cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, nor demonstrates the effect of the peptide in the treatment of a specific disease, the invention is highly unpredictable regarding the outcome of the treatment using a cyclized conotoxin peptide which does not have a defined sequence.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a cyclized conotoxin peptide having no free N- and C-termini, a process of preparing the cyclic conotoxin, a composition comprising the cyclic conotoxin, a method of using the cyclic conotoxin as a neuropharmacological probe, and a method of treatment or prophylaxis of diseases comprising administering the cyclized conotoxin peptide. The specification indicates the preparation of cyclic MVIIA conotoxins (Examples 1, 2) and cyclic MII α-conotoxins (Example 6), and the cyclic MVIIA conotoxins act as the antagonists specific for N-type voltage-sensitive calcium channels (Example 3). The specification also indicates omega-conotoxins which block N-type calcium channels may be useful for the treatment of neurological disorders (page 15, line 23-page 16, line 1). However, the specification has not shown various cyclized conotoxin peptides other than cyclic MVIIA conotoxins and cyclic MII α-conotoxins. Furthermore, the specification has not demonstrated the use of any cyclized peptide in the treatment of specific diseases. There are no working examples indicating the effects of the cyclized conotoxin peptides in treating various diseases. Since the specification has not provided sufficient teachings on identities of various cyclized conotoxin peptides and the treating conditions such as the dose and the time for treating specific diseases, thus, it is necessary to have additional guidance on amino acid sequences of various cyclized conotoxin peptides, and the treatment of various diseases using the cyclized conotoxin peptides, and to carry out further experimentation to assess the effects of various cyclized conotoxin peptides in the treatment of specific diseases.

(6). Nature of the Invention

The scope of the claims encompass a cyclized conotoxin peptide and a method of treatment or prophylaxis of diseases comprising administering the cyclic conotoxin, but the specification only shows the making of cyclic MVIIA conotoxins and cyclic MII α-conotoxins, and the cyclic MVIIA conotoxins acting as the antagonists specific for N-type voltage-sensitive calcium channels, it has not demonstrated the use of any cyclized conotoxin peptide in the treatment of specific diseases. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the outcome of treatment is unpredictable using the claimed variants, and the guidance and the teaching are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the cyclized conotoxin in the treatment of diseases.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 3, 7 and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 3 and 7 are indefinite because of the use of the term "derivative thereof" or "derived from". The term "derivative thereof" or "derived from" renders the claim indefinite, it is unclear what amino acid sequence the derivative has, and how different the derivative or the

linear conotoxin peptide moiety derived from a naturally occurring conotoxin peptide is as compared to the parent conotoxin peptide.

7. Claim 13 is indefinite because of the use of the term "if required". The term "if required" renders the claim indefinite, it is unclear whether both cyclizing the extended peptide and oxidizing to form disulfide bonds are required or not, or, only oxidizing to form disulfide bonds is required.

8. Claims 14 and 16 provide for the use of a cyclic conotoxin peptide but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

9. Claim 15 is indefinite because the claim lacks essential steps as claimed in the process of treatment or prophylaxis of conditions or diseases. The omitted steps are the effective amount of the cyclic conotoxin peptide administered and the outcome of the treatment. Claims 15 and 16 are also indefinite because of the use of the term "conditions or diseases". The term "conditions or diseases" renders the claim indefinite, it is unclear what the conditions or diseases are.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Olivera *et al.* (U. S. Patent 4,447,356).

Olivera *et al.* teach conotoxin GI (claim 4), a naturally occurring conotoxin (claim 3), has the sequence Glu-Cys-Cys-Asn-Pro-Ala-Cys-Gly-Arg-His-Tyr-Ser-Cys-NH_2, where disulfide bonds form between two cysteines at positions 2 and 7, and at positions 3 and 13, which indicates its cyclic structure and has no free C-terminus (abstract, column 2, lines 2-26; claim 1). The conotoxin is active on a wide range of vertebrate animals including humans and is useful for reversibly immobilizing a muscle or groups of muscles in humans (column 2, lines 39-43; claims 2, 15 and 16).

11. Claims 1, 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Pallaghy *et al.* (Protein Science 3, 1833-1839 (1994)).

Pallaghy *et al.* teach the 3-dimensional structure of ω-conotoxin GVIA (*Conus geographus*, claim 3), the ω-CgTx GVIA contains a C-terminus amide group (Fig. 1) and three disulfide bonds forming a cystine knot and a cyclic structure (page 1833, right column, page 1834, left column; claims 1, 3 and 5).

12. Claims 1-5 and 14-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Shon *et al.* (WO 96/33206).

Shon *et al.* teach Conotoxin peptides such as δ-conotoxin PVIA and μ-conotoxin PIIIA (claims 3 and 4) have 25-35 amino acids, and six cysteines forming three disulfide bonds between the first and fourth, second and fifth, and third and sixth cysteines, respectively (claim 5), which indicates the cyclic structures. The C-terminus of δ-conotoxin PVIA (SEQ ID NO:1 of WO 96/33206) may be amidated, and μ-conotoxin PIIIA (SEQ ID NO:2 of WO 96/33206) has

an amide group at C-terminus (page 4, lines 10-22; claim 1). The μ-conotoxin PIIIA is a sodium channel blocker and is useful as active agent for muscle contraction in instances where lack of muscle contraction is problematic such as for treating urinary or fecal incontinence, it is also useful as anti-seizures or anti-neoplastic agents (page 8, lines 19-page 9, line 2; claims 2, 14-16).

13. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

14. Claims 1-9 and 11-18 are rejected and claim 10 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. C'K
Patent Examiner

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April 2, 2003

Christopher S. Low

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